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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07F 9/6571, 9/6574, 9/40, A61K 31/665 — A1

(11) International Publication Number: WO 98/25938

(43) International Publication Date: 18 June 1998 (18.06.98)

(21) International Application Number: PCT/SE97/02052

(22) International Filing Date: 9 December 1997 (09.12.97)

(30) Priority Data:
9604582-8 13 December 1996 (13.12.96) SE

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS

(57) Abstract

The present invention pertains to novel compounds which are derivatives of phosphonoformic acid, processes for their synthesis and their use as antiviral agents.

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NOVEL COMPOUNDS

Field of the invention

The present invention relates to novel compounds, novel methods for their preparation, novel intermediates, pharmaceutical compositions and to methods for combatting viral diseases caused by, for example, herpesviruses or retroviruses, which can occur in animals including man. Such diseases include both common viral infections and virus-related neoplastic diseases.

Background of the invention

Phosphonoformic acid (PFA) is a well known compound having antiviral activity. Pharmaceutical formulations of PFA for the treatment of viral diseases have been described in U.S. Patent Nos. 4,215,113; 4,339,445; 4,665,062 and 4,771,041. PFA inhibits replication of all known herpesviruses in vitro including cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV) and varicella-zoster virus (VZV) as well as certain retroviruses including the human immunodeficiency virus (HIV) types 1 and 2 (HIV-1 and HIV-2).

Alkyl derivatives of PFA are known from EP 0 003 007 and from Norén, J.-O. et al. (J. Med. Chem. 26 (1983) 264-270) and amide derivatives of PFA are known from EP 0 003 008, as are the antiviral effects in vitro and in vivo in animals of such compounds and of pharmaceutical compositions thereof. So far, however, no drug based on any of these alkyl or amide derivatives has become availiable.

Phosphonoformic acid hydrazides are known from US 4,308,263 as are the antiviral effects against herpesviruses in vitro of such compounds. So far, however, no drug based on any of these hydrazides has become available.

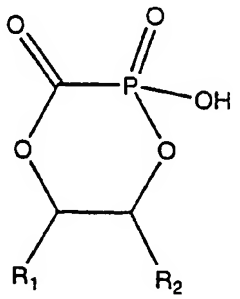
Lipid derivatives of phosphonoacids for liposomal incorporation are known from WO 95/13682 and from Hostetler, K. Y. et al., Antiviral Research 31 (1996), 59-67, as are the antiviral effects in vitro of such compounds on viruses such as HIV, hepatitis B virus, EBV, and VZV.

P-monoesters of foscarnet with octadecyl substituted alditol moieties as well as with substituted derivatives of glycerol have been disclosed in WO 96/15132.

Treatment of CMV infections in AIDS patients infected with herpesvirus with foscarnet, i.e. trisodium phosphonoformate hexahydrate, is at present by intravenous injections. This mode of treatment is burdensome where foscarnet must be administered daily. Doses in the range of grams per day need to be administered. The development of a more effective drug is therefore very desirable since it would offer a more convenient method of treatment and result in improved quality of life for the patient.

Description of the invention

According to the invention we provide compounds of formula I

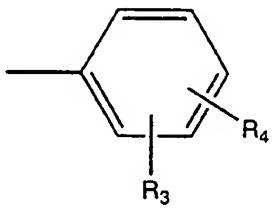


I

wherein R_1 and R_2 each independently are hydrogen, or a C_{1-24}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-24}-alkyl, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkoxy-C_{1-24}-alkyl, C_{1-24}-alkylthio-C_{1-24}-alkyl group and each C_{1-24}-alkyl or -alkoxy group may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds, and is optionally

substituted with one or more hydroxy, mercapto, amino, halogen, oxo, or with C_{1-24}-alkoxy, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkoxycarbonyloxy, C_{1-24}-alkylthio, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkoxycarbonylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino, C_{1-24}-alkoxycarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkoxycarbonyl)amino, and each C_{1-24} -alkyl or -alkoxy group may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

or wherein R_1 and R_2 each independently are carboxyl, carboxamido, aryl, aryloxycarbonyl, or aryl-C_{1-24}-alkyl, C_{1-24}-alkoxycarbonyl, C_{1-24}-alkylaminocarbonyl, di-(C_{1-24}-alkyl)aminocarbonyl, aryl-C_{1-24}-alkoxycarbonyl, aryl-C_{1-24}-alkylaminocarbonyl, C_{1-24}-alkylcarbonyloxymethoxycarbonyl, C_{1-24}-alkylcarbonyloxy-(C_{1-4}-alkyl)methoxycarbonyl, C_{1-24}-alkoxycarbonyloxymethoxycarbonyl, C_{1-24}-alkoxycarbonyloxy-(C_{1-4}-alkyl)-methoxycarbonyl, all the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds and all the C_{1-4}-alkyl groups of which may be branched or unbranched and saturated or unsaturated, and where each aryl group has the formula II



II

wherein R_3 and R_4 are the same or different and each is selected from the group consisting of hydrogen, halogen, or C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-acyl, C_{1-4}-acyloxy, C_{1-4}-alkoxycarbonyl, all of which may be branched or unbranched; or R_3 and R_4 together form an unbranched saturated alkylene chain having 3 or 4 carbon atoms bound to adjacent positions in the phenyl ring; or R_3 and R_4 together form a methylenedioxy group, a 1,1-

ethylidenedioxy group, or a 1,2-ethylenedioxy group bound to adjacent positions of the phenyl ring;

or wherein R_1-CH-CH-R_2 form part of a C_{4-8}-carbocyclic ring which is optionally substituted with hydroxy, mercapto, amino, halogen, oxo, or with C_{1-24}-alkyl, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonyl, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkoxycarbonyl, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino, all the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

or wherein R_1-CH-CH-R_2 form part of the furanose or pyranose ring of a sugar, e.g. D-ribose, D-arabinose, D-xylose, D-lyxose, D-glucose, D-galactose, D-mannose, D-talose, D-allose, D-altrose, D-gulose, D-idose or the corresponding L-isomers, the hydroxyl groups of which may optionally be replaced by hydrogen, halogen, amino, azido, oxo, mercapto, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

and physiologically acceptable salts and optical isomers thereof.

Preferred are compounds of formula I wherein R_1 and R_2 each independently are hydrogen or methyl which latter is optionally substituted with hydroxy or mercapto, or with C_{1-24}-alkoxy, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkylthio, or C_{1-24}-alkylcarbonylthio, the C_{1-24}-alkyl and -alkoxy groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds.

More preferred are compounds of formula I wherein R_1 is as defined immediately above except hydrogen, and R_2 is hydrogen.

Also more preferred are compounds of formula I wherein R_1 and R_2 each independently are hydrogen or *n*-octadecyloxymethyl.

Especially preferred are compounds of formula I wherein R_1 is *n*-octadecyloxymethyl and R_2 is hydrogen.

Particularly preferred is the compound of formula I wherein R_1 is *n*-octadecyloxymethyl, R_2 is hydrogen and the configuration is (R).

The compounds of the invention are useful in therapeutic and /or prophylactic treatment of viral infections and may be useful in therapeutic and/or prophylactic treatment of virus-related neoplastic diseases in mammals.

The compounds of the present invention are particularly useful for the treatment of human herpesvirus infections and human retrovirus infections. They are also useful for the treatment of viral infections associated with acquired immunodeficiency syndrome (AIDS). The human herpesviruses include HSV-1 and HSV-2, VZV, CMV, EBV, human herpesvirus 6 and 7(HHV-6 and HHV-7), and human herpesvirus 8 (HHV-8) also known as Kaposi's sarcoma associated herpesvirus (KSHV). Human retroviruses include human immunodeficiency virus type 1 and 2 (HIV-1 and HIV-2) and human T-cell leukaemia virus type 1 and type 2 (HTLV-1 and HTLV-2). Another important area of use of the compounds of the present invention is in the treatment of infections caused by ortho-myxoviruses, e.g. influenza viruses of type A and type B. A further area of use is in the treatment of infections caused by viruses such as hepatitis B virus and hepatitis C virus, papillomaviruses, adenoviruses and poxviruses.

Other possible areas of use of the compounds of the present invention are in the treatment of infections caused by picornaviruses, arboviruses, arenaviruses, coronaviruses, rhabdoviruses, paramyxoviruses and bunyaviruses.

Pharmaceutical formulations

The compounds according to the invention may be used for the therapeutic and prophylactic control and treatment of diseases caused by virus infections. The compounds of the invention can be used alone or with other antiviral agents, e.g. acyclovir, valacyclovir, famciclovir, penciclovir, desciclovir, brivudine, carbovir, fiacitibine, ibacitabine, ganciclovir, idoxuridine, sorivudine, trifluridine, vidarabine, cidofovir, lobucavir, afovirsen, zidovudine, didanosine, stavudine, zalcitabine, dideoxyadenosine, lamivudine, FTC, fialuridine, adefovir, adefovir dipivoxil, nevirapine, delaviridine, loviride, saquinavir, indinavir, ritanovir, nelfinavir, 141W94, ribavirin, amantidine, rimantidine, sICAM-1, pirodavir, GG167, 1263W94, fomivirsen, GEM-132, RS-79070, SR-3775, or with immunological agents e.g. antiinflammatory agents including steroids, in particular glucocorticoids, and non-steroid antiinflammatory drugs (NSAID's), CMV neutraGAM, regavirumab, sevirumab, interferon, and growth factors e.g. granulocyte-macrophage (GM-CSF) and granulocyte-colony stimulating factors (G-CSF).

The compounds of the present invention are suitably admixed with excipients to be formulated into capsules, tablets, suppositories and other formulations, e.g. ointments, suspensions, gels and solutions.

For clinical use the compounds of the invention may be formulated into pharmaceutical formulations for oral, parenteral, rectal and topical administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable excipient. The excipient may be in the form of a solid, semi-solid or liquid diluent. Usually the amount of active compound is between 0.1-99% by weight of the preparation.

In the preparation of pharmaceutical formulations containing the compounds of the present invention in the form of dosage units for oral administration the compound may be mixed

with a solid, powdered carrier, e.g. lactose, sucrose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier; stabilizing substances, e.g. alkaline compounds, e.g. bicarbonates, carbonates, and hydroxides of sodium, potassium, calcium, magnesium, as well as magnesium oxide and the like as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture may then be processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-coating polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Soft gelatin capsules may also be enteric-coated as described above.

Hard gelatin capsules may also contain the active compound in combination with a powdered carrier as described above. The hard gelatin capsules may be enteric-coated as described above. Hard gelatin capsules may contain granules or enteric-coated granules of the active compound.

Dosage units for rectal administration may be prepared in the form of suppositories with the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatin capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules, or they may be prepared in the form of enemas, e.g. dry micro enemas, or they may be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of solutions, syrups, emulsions or suspensions, e.g. containing from 0.1% to 50% by weight of the active ingredient and the remainder consisting of for example sugar or an alditol and/or a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin or carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

In addition, using known pharmaceutical procedures, sustained release preparations at doses of 1 mg to 2000 mg may be formulated.

For topical application, especially for the treatment of herpes virus infections on skin, genitals and in mouth and eyes the preparations are suitably in the form of a solution, ointment, gel, suspension cream or the like. The amount of active substance may vary, for example between 0.05% to 20% by weight of the preparation . Such preparations for topical application may be prepared in known manner by mixing the active substance with known carrier materials e.g. isopropanol, glycerol, paraffin, stearyl alcohol, polyethylene glycol, etc. The pharmaceutically acceptable carrier may also include a known chemical absorption promotor. Examples of absorption promotors are e.g. dimethylacetamide, trichloroethanol or trifluoroethanol, certain alcohols and mixtures thereof.

Liposomal formulations based on lipid substances, e.g. phospholipids, sphingolipids, glycolipids, and galactolipids can be used for formulations for oral, topical or parenteral administration.

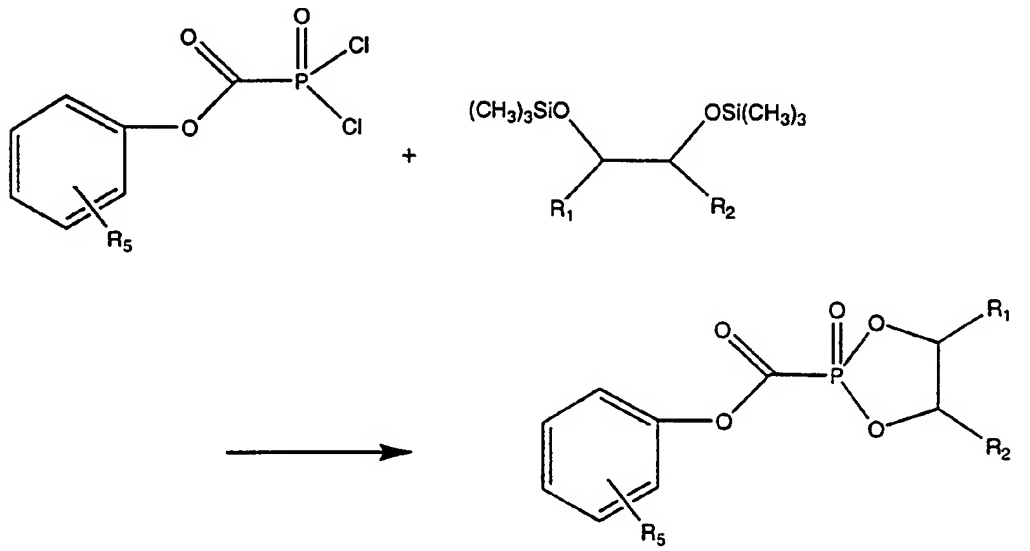
The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, doses will be in the range of 1 mg to 2000 mg per day, preferably 5 mg

to 1000 mg of active substance per day. Unit doses of 0.25 mg to 2000 mg can be given e.g. 1 to 4 times a day.

Methods of preparation of the compounds

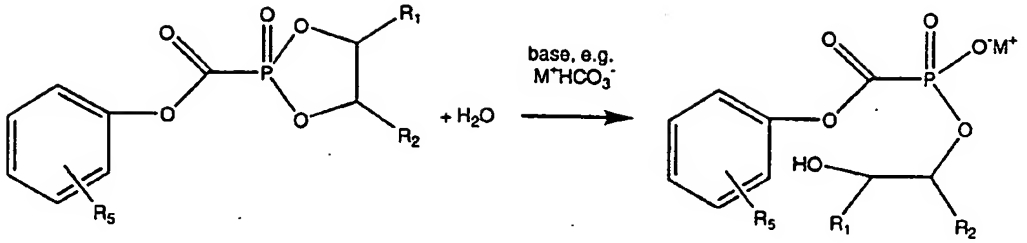
The compounds of the formula I may be prepared by cyclization of suitably substituted *P,C*-diesters of phosphonoformic acid, for example as follows.

Reacting a suitably substituted aryloxycarbonylphosphonic dichloride with the bis-trimethylsilyl ether of a *vic*-diol to give a cyclic triester of phosphonoformic acid (a 1,3,2-dioxaphospholane) according to the formula:



III

followed by hydrolysis with one equivalent of water and subsequent neutralization, e.g. by addition of one equivalent of a base according to the formula:



III IV

and finally by cyclization to give a salt of a compound of the formula I.

In order to liberate the free acid, the salt may be treated with an acidic ion exchange resin in a suitable solvent, e.g. ethanol or water.

R_1 and R_2 have the meaning given above and R_5 is an electron-withdrawing group, e.g. carbomethoxy, carboethoxy, acetyl, or nitro at the *ortho*- or *para*-position of the phenyl ring. However, if R_1 and R_2 contain groups with labile hydrogen atoms, e.g. carboxyl, hydroxyl, mercapto or amino, they must first be protected with suitable protective groups which can be subsequently removed. Examples of such protective groups and methods for their introduction and removal are given in Protective Groups in Organic Synthesis, Ed. T. W. Greene and P.G. M. Wuts, John Wiley & Sons, Inc., New York, 1991. M^+ is a cation, e.g. Li^+, Na^+, K^+, Et_3NH^+ or $C_5H_5NH^+$.

The compounds of formulas III and IV are novel and are comprised in the scope of the present invention.

The first step of the reaction may be carried out in a suitable solvent, e.g. tetrahydrofuran or dioxane, at a temperature from 0°C to the boiling point of the solvent for 2 hours to 7 days. The aryloxycarbonylphosphonic dichlorides required as starting materials are prepared by methods known *per se* for the synthesis of dichlorides of phosphoric acids and phosphonic acids. References for these methods are found, for example, in L.A. Slotin, Synthesis 1977, 737 and in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII/1, p. 387-406 and Band XII/2, p. 212-225. The bis-trimethylsilyl ethers may be obtained by

methods known *per se* for the trimethylsilylation of alcohols. References for these methods are found, for example, in Protective Groups in Organic Chemistry, Ed. T.W. Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 1991, p. 68-71.

The second step of the reaction (hydrolysis of the cyclic phosphonoformate ester) may be carried out in a suitable solvent, e.g. tetrahydrofuran or dioxane, at a temperature from 0°C to the boiling point of the solvent for 5 minutes to 2 hours followed by neutralization with e.g. one equivalent of a base, e.g. sodium, potassium, or lithium bicarbonate, carbonate or hydroxide, or an amine, e.g. triethylamine or pyridine.

The final step of the reaction may be carried out in a suitable solvent, e.g. dimethyl-formamide or dimethyl sulfoxide, in the presence of a suitable base, e.g. 1,5-diaza-bicyclo[4.3.0]non-5-ene or 1,8-diazabicyclo[5.4.0]undec-7-ene, at a temperature from 0°C to 100°C for 1 hour to 48 hours.

Experimental part

General experimental procedures

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker AC-F200 (^{1}H = 200 MHz), on a Bruker AM 400 (^{1}H = 400 MHz), or on a Jeol GSX-270 (^{1}H=270 MHz) spectrometer. The spectra were referenced to tetramethylsilane (^{1}H), 85% H_3PO_4 (^{31}P), $CDCl_3$ or DMSO-d_6 (^{13}C). ^{31}P and ^{13}C NMR spectra were ^{1}H decoupled, unless otherwise stated. Coupling constants are given in Hz. Mass spectra were recorded on a Fisons VG Quatro quadrupole mass spectrometer or on a Jeol JMS-SX102 mass spectrometer. The following solvents and chemicals were purified before use by heating under reflux and distillation over the appropriate drying agent: toluene and trimethyl phosphite (Na), diethyl ether and dioxane (CaH_2), pyridine (BaO), dichloromethane, acetonitrile and dimethylformamide (P_2O_5). Tetrahydrofuran (THF) was purified by treatment overnight with KOH, heating under reflux and distilling from potassium.

A detailed description of the synthesis of the intermediate and final compounds according to the present invention follows. The title compound of each example was obtained according to the description.

Example 1

2-Ethoxycarbonylphenyl chloroformate:

A mixture of 16.6 g (0.1 mol) ethyl salicylate and 7.9 g (0.1 mol) dry pyridine in 50 ml of dry toluene was added dropwise to a solution of phosgene (12g, 0.12 mol) in 120 ml of dry toluene at -5° C with stirring for 1 h. The reaction mixture was stirred for 2 h at room temperature, cooled to 0° C and 15 ml of chilled 10% aq. HCl was added dropwise. The organic layer was separated, dried over $CaCl_2$ and distilled *in vacuo* to give 17.8 g (78%) colourless liquid (b.p. 114° C at 5 mm Hg). δ_H ($CDCl_3$): 1.42 (t, 3H, OC_2H_5); 4.42 (q, 2H, OC_2H_5); 7.27 (dd, 1H, arom. 3-CH); 7.41 (dt, 1H, arom. 4-CH); 7.58 (dt, 1H, arom. 5-CH) and 8.08 (dd, 1H, arom. 6-CH).

Example 2

Dimethyl [(2-ethoxycarbonylphenoxy)carbonyl]phosphonate:

A solution of 2.29 g (10 mmol) 2-ethoxycarbonylphenyl chloroformate and 1.24 g (10 mmol) trimethyl phosphite in 10 ml toluene was heated under reflux with stirring for 3 h under argon and left overnight at room temperature. Toluene was removed at reduced pressure and the residue was kept for 16 h at 1 mm Hg and room temperature. A clear colourless liquid resulted, yield 2.54 g (84%). δ_H ($CDCl_3$): 1.37 (t, 3H, OC_2H_5); 4.04 (d, 6H, 2 x OCH_3, J_{PH} 11); 4.35 (q, 2H, OC_2H_5); 7.15 (dd, 1H, 3-CH); 7.35 (dt, 1H, 4-CH); 7.58 (dt, 1H, 5-CH) and 8.08 (dd, 1H, 6-CH). δ_P ($CDCl_3$): -2.39 (s). δ_C ($CDCl_3$): 13.58 (s, $OCH_2\underline{C}H_3$); 54.46 (d, J_{PC} 5.5, 2 x OCH_3); 60.38 (s, $O\underline{C}H_2CH_3$); 122.89 (s, aromatic CH);

126.47 (s, aromatic CH); 131.32 (s, aromatic CH); 133.55 (s, aromatic CH); 148.65 (d, J_{PC} 6.5, aromatic CH); 163.04 (s, C=O) and 164.41 (d, J_{PC} 273.2, C=O).

Example 3

Bis(trimethylsilyl) [(2-ethoxycarbonylphenoxy)carbonyl]phosphonate

Bromotrimethylsilane (6.12 g, 40 mmol) was added dropwise within 1 h to 6.04 g (20 mmol) of dimethyl [(2-ethoxycarbonylphenoxy)carbonyl]phosphonate with stirring at room temperature under argon. After stirring for an additional 4 h, volatiles were removed at reduced pressure (1 h at 1 mm Hg). The resulting colourless liquid was used without further purification. Yield 8.2 g (98%). δ_H ($CDCl_3$): 0.39 (s, 18H, 2 x $SiMe_3$); 1.38 (t, 3H, OC_2H_5); 4.34 (q, 2H, OC_2H_5); 7.13 (d, 1H, arom. 3-CH); 7.32 (t, 1H, arom. 4-CH); 7.52 (t, 1H, arom. 5-CH) and 8.02 (d, 1H, arom. 6-CH). δ_P ($CDCl_3$): -22.62 (s).

Example 4

[(2-Ethoxycarbonylphenoxy)carbonyl]phosphonic dichloride

To 4.18 g (10 mmol) of bis(trimethylsilyl) [(2-ethoxycarbonylphenoxy)carbonyl]-phosphonate, freshly distilled thionyl chloride (5 ml) was added and the reaction mixture was heated under argon at 70° C for 4 h. Excess thionyl chloride and chlorotrimethylsilane were distilled off and the residue was kept under vacuum (1 mm Hg) at 80° C for 2 h. A clear yellowish liquid resulted, yield 2.95 g (94%). δ_H ($CDCl_3$): 1.33 (t, 3H, OC_2H_5); 4.28 (q, 2H, OC_2H_5); 6.83 (dd, 1H, arom. 3-CH); 7.08 - 7.23 (m, 2H arom. 4-CH, 5-CH); 8.05 (dd, 1H, arom. 6-CH). δ_P (THF): 10.54 (s). δ_P ($CDCl_3$): 12.06 (s).

Example 5

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-1,3,2-dioxaphospholane-2-oxide

A solution of 1.03 g (5 mmol) 1,2-bis(trimethylsilyloxy)ethane in 10 ml of dry THF was added dropwise to a stirred solution of 1.56 g (5 mmol) [(2-ethoxycarbonylphenoxy)-carbonyl]phosphonic dichloride in 10 ml of dry THF at room temperature under argon. The reaction mixture was stirred for an additional 1 h, then solvent and chlorotrimethylsilane were removed under reduced pressure under dry conditions to give a clear viscous liquid (1.41 g, 94%). δ_H ($CDCl_3$): 1.34 (t, 3H, OC_2H_5); 4.32 (q, 2H, OC_2H_5); 4.67 (d, 4H, J_{PH} 9.5, $-CH_2CH_2-$); 7.16 (d, 1H, arom. 3-CH); 7.38 (t, 1H, arom. 4-CH); 7.59 (t, 1H, arom. 5-CH) and 8.08 (d, 1H, arom. 6-CH). δ_P ($CDCl_3$): 13.15 (s).

The compounds in the following Examples 6 - 8 were prepared in a similar manner to that described in Example 5 from [(2-ethoxycarbonylphenoxy)carbonyl]phosphonic dichloride and the appropriate bis(trimethylsilyl) ether.

Example 6

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-dodecanoyloxymethyl-1,3,2-dioxa-phospholane-2-oxide

The starting bis(trimethylsilyl) ether, 1,2-bis(trimethylsilyloxy)-3-dodecanoyloxypropane, was prepared by silylation of 3-dodecanoyloxy-1,2-propanediol by conventional methods.

Two diastereomers were obtained in the ratio 1:1 as racemates. δ_P ($CDCl_3$): 11.89 (s) and 12.25 (s).

Example 7

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-octanoylthiomethyl-1,3,2-dioxaphospholane-2-oxide

The starting bis(trimethylsilyl) ether, 1,2-bis(trimethylsilyloxy)-3-octanoylthiopropane, was prepared by silylation of 3-octanoylthio-1,2-propanediol by conventional methods.

Two diastereomers were obtained in the ratio 1:1 as racemates. δ_P ($CDCl_3$): 11.96 (s) and 12.32 (s).

Example 8

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-dodecanoylthiomethyl-1,3,2-dioxaphospholane-2-oxide

The starting bis(trimethylsilyl) ether, 1,2-bis(trimethylsilyloxy)-3-dodecanoylthiopropane, was prepared by silylation of 3-dodecanoylthio-1,2-propanediol by conventional methods.

Two diastereomers were obtained in the ratio 1:1 as racemates. δ_P ($CDCl_3$): 11.88 (s) and 12.25 (s).

Example 9

Sodium 2-hydroxyethyl [(2-ethoxycarbonylphenoxy)carbonyl]phosphonate

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-1,3,2-dioxaphospholane-2-oxide (1.5 g, 5 mmol) was dissolved in 20 ml dioxane containing 0.090 g (5 mmol) of water with stirring at room temperature, then 5 ml of 1M aqueous sodium bicarbonate was added dropwise. The solvents were evaporated and the residue was dried *in vacuo* (1 mm Hg) for 6 h giving a

colourless glass (1.6 g, 95%). δ_H (DMSO-d_6): 1.29 (t, 3H, OC_2H_5); 3.52 (dt, 2H, $C\underline{H}_2OH$); 3.89 (dt, 2H, J_{PH} 12, $POCH_2$); 4.25 (q, 2H, OC_2H_5); 7.11 (d, 1H, arom. 3-CH); 7.38 (t, 1H, arom. 4-CH); 7.62 (t, 1H, arom. 5-CH) and 7.86 (d, 1H, arom. 6-CH). δ_P (dioxane, DMSO-d_6 insert): -5.52 (s).

The compounds in the following Examples 10 - 12 were prepared in a similar manner to that described in Example 9.

Example 10

Sodium 3-dodecanoyloxy-2-hydroxypropyl [(2-ethoxycarbonylphenoxy)-carbonyl]phosphonate

Starting material: 2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-dodecanoyloxymethyl-1,3,2-dioxaphospholane-2-oxide.

Yield 92%. δ_P (acetone, DMSO-d_6 as external standard): -3.22 (s).

Example 11

Sodium 3-octanoylthio-2-hydroxypropyl [(2-ethoxycarbonylphenoxy)-carbonyl]phosphonate

Starting material: 2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-octanoylthiomethyl-1,3,2-dioxaphospholane-2-oxide

Yield 84% (after washing with acetone). δ_P (DMSO-d_6): -5.72 (s).

Example 12

Sodium 3-dodecanoylthio-2-hydroxypropyl [(2-ethoxycarbonylphenoxy)-carbonyl]phosphonate

Starting material: 2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-dodecanoylthiomethyl-1,3,2-dioxaphospholane-2-oxide

Yield 92%. δ_P (DMSO-d_6): -5.82.

Example 13

Sodium 2-hydroxy-1,4,2-dioxaphosphorinane-2,3-dioxide

Sodium 2-hydroxyethyl [(2-ethoxycarbonylphenoxy)carbonyl]phosphonate (1.7 g, 5 mmol) was dissolved in 10 ml dry DMF and 30 mg 1,8-diazabicyclo[5.4.0]undec-7-ene was added to the solution. The reaction mixture was stirred for 6 h at room temperature, then poured into 200 ml of dry ether. The precipitate was filtered and washed with acetone (2 x 50 ml) resulting in 1.4 g (81%) of a white crystalline powder. δ_H (D_2O): 4.28 (ddt, 2H, J_{PH} 13.74, J_{H6H5} 4.57, $J_{H6H6'}$ 1.71, 6-H); 4.43 (dt, 2H, J_{H5H6} 4.55, $J_{H5H5'}$ 2.28, 5-H). δ_P (D_2O): -7.84 (s). δ_C (D_2O): 65.82 (d, J_{PC} 6.2, 6-C) and 70.84 (d, J_{PC} 5.6, 5-C); m/z: 157.2 (M- Na^+).

The compounds in the following Examples 14 - 16 were prepared in a similar manner to that described in Example 13.

Example 14

Sodium 2-hydroxy-5-dodecanoyloxymethyl-1,4,2-dioxaphosphorinane-2,3-dioxide

Starting material: Sodium 3-dodecanoyloxy-2-hydroxypropyl[2-ethoxycarbonyl-phenoxy)carbonyl]phosphonate

Yield 64%. δ_P (DMSO-d_6): -9.54 (s). δ_H (D_2O/DMSO-d_6): 0.88 (t, 3H, CH_3); 1.25 (br m, 16H, $(CH_2)_8$); 1.57 (m, 2H, $COCH_2\underline{CH_2}$); 2.25 (t, 2H, $COCH_2$); 3.33 (dt, 2H, CH_2OCO); 4.05 - 4.40 (m, 3H, 5-H & 6-H).

Example 15

Sodium 2-hydroxy-5-octanoylthiomethyl-1,4,2-dioxaphosphorinane-2,3-dioxide

Starting material: Sodium 3-octanoylthio-2-hydroxypropyl[(2-ethoxycarbonylphenoxy)carbonyl]phosphonate

Yield 72%. δ_P (D_2O): -8.15 (s). δ_H (D_2O): 0.98 (t, 3H, CH_3); 1.38 (br s, 8H, 4 x CH_2); 1.77 (m, 2H, $COCH_2\underline{CH_2}$); 2.75 (t, 2H, $COCH_2$); 3.42 (d, 2H, SCH_2); 4.43 - 4.68 (m, 2H, 6-H) and 4.96 (m, 1H, 5-H). δ_C (D_2O): 12.98 (s, CH_3); 21.58; 24.56; 27.83; 28.03; 28.22; 30.83 (6s, $(CH_2)_6$); 42.92 (s, SCH_2); 66.11 (d, J_{PC} 4.5, 6-C); 77.73 (s, 5-C); 172.79 (d, J_{PC} 205.7, 3-C) and 199.21 (s, SCO).

Example 16

Sodium 2-hydroxy-5-dodecanoylthiomethyl-1,4,2-dioxaphosphorinane-2,3-dioxide

Starting material: Sodium 3-dodecanoylthio-2-hydroxypropyl[(2-ethoxycarbonylphenoxy)carbonyl]phosphonate

Yield 84%. δ_P (DMSO-d_6): -9.57 (s). δ_H (DMSO-d_6): 0.87 (t, 3H, CH_3); 1.22 (br s, 16H, $(CH_2)_8$); 1.54 (m, 2H, $COCH_2\underline{CH_2}$); 2.62 (t, 2H, $COCH_2$); 3.13 (t, 2H, SCH_2); 3.96 - 4.18 (m, 2H, 6-CH_2) and 4.63 (m, 1H, 5-CH). δ_C (DMSO-d_6): 13.91 (s, CH_3); 22.06; 24.96; 28.17; 28.41; 28.59; 28.66; 28.78; 28.93; 29.00; 31.26 (10 s, $(CH_2)_{10}$); 65.43 (d, J_{PC} 6.0, 6-C); 76.29 (s, 5-C); 174.56 (d, J_{PC} 196.2, 3-C) and 197.94 (s, SCO).

Example 17

2-[(2-Ethoxycarbonylphenoxy)carbonyl]-4-octadecyloxymethyl-1,3,2-dioxaphospholane-2-oxide

The starting bis(trimethylsilyl) ether, 1,2-bis(trimethylsilyloxy)-3-octadecyloxypropane, was prepared by silylation of 3-octadecyloxy-1,2-propanediol (batyl alcohol) by conventional methods.

A solution of 3.5 g (7.1 mmol) 1,2-bis(trimethylsilyloxy)-3-octadecyloxypropane in 15 ml of dry THF was added dropwise to a stirred solution of 2.23 g (7.1 mmol) [(2-ethoxycarbonylphenoxy)carbonyl]phosphonic dichloride in 10 ml of dry THF at room temperature under argon. The mixture was stirred for a further 1 h, then concentrated under reduced pressure to give a clear oil. The product was used directly in the following Example 18.

Example 18

Sodium 3-octadecyloxy-2-hydroxypropyl [(2-ethoxycarbonylphenoxy)carbonyl]-phosphonate

The product of Example 17, 2-[(2-ethoxycarbonylphenoxy)carbonyl]-4-octadecyloxymethyl-1,3,2-dioxa-phospholane-2-oxide, was dissolved in 30 ml dioxane containing 0.13

ml (7.1 mmol) of water with stirring at room temperature, then 7.1 ml of 1M aqueous sodium bicarbonate was added dropwise during 30 min. The solvents were evaporated and the residue was dried under reduced pressure to give a dry foam (4.29 g), which was extracted twice by stirring with warm ether. After cooling the ether extracts, the product was collected by filtration to give 2.91 g (76%) of a solid product. δ_P (DMSO-d_6): -5.98 (s).

Example 19

Sodium 2-hydroxy-5-octadecyloxymethyl-1,4,2-dioxaphosphorinane-2,3-dioxide

Sodium 3-octadecyloxy-2-hydroxypropyl [(2-ethoxycarbonylphenoxy)carbonyl]-phosphonate (1.5 g, 2.78 mmol) was dissolved in 6 ml dry DMF and 17 mg 1,8-diaza-bicyclo[5.4.0]undec-7-ene was added. The reaction mixture was stirred for 6 h at room temperature, then poured into 120 ml dry ether. The precipitate was filtered off to afford 0.9 g (88%) of a white crystalline powder. δ_P (DMSO-d_6): -9.91 (s). FAB-MS: m/z 457.37 ($M + H^+$).

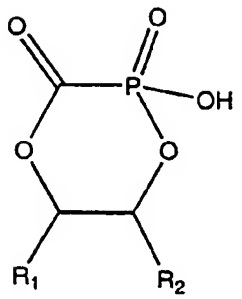
Tests for antiviral activity

The antiviral activity of the compounds of the invention may be determined according to the method of Wahren, B. et al., J. Virol. Methods 6 (1983) 141-149. Thus confluent human lung fibroblast cells are infected with Herpes simplex virus type 1 (HSV-1). After absorption for one hour at 37°C, virus is removed and the compounds of the invention diluted in cell media were added, at concentrations of 800 µM down to 3 µM. Cells are incubated at 37°C in a humidified atmosphere of 5% CO_2 in air until a characteristic cytopathic effect is seen in control wells (24-48 h). Cells are lysed by addition of Triton X-100, and viral antigen content of the supernatants measured by enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody.

Some of the compounds of the invention were tested according to this test method for antiviral activity and were all found to be active.

Claims

1. A compound of the formula I

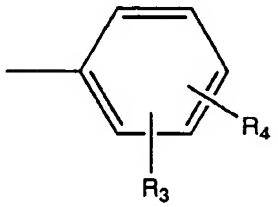


I

wherein R_1 and R_2 each independently are hydrogen, or a C_{1-24}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-24}-alkyl, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkoxy-C_{1-24}-alkyl, C_{1-24}-alkylthio-C_{1-24}-alkyl group and each C_{1-24}-alkyl or -alkoxy group may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds, and is optionally substituted with one or more hydroxy, mercapto, amino, halogen, oxo, or with C_{1-24}-alkoxy, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkoxycarbonyloxy, C_{1-24}-alkylthio, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkoxycarbonylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino, C_{1-24}-alkoxycarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkoxycarbonyl)amino, and each C_{1-24} -alkyl or -alkoxy group may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

or wherein R_1 and R_2 each independently are carboxyl, carboxamido, aryl, aryloxycarbonyl, or aryl-C_{1-24}-alkyl, C_{1-24}-alkoxycarbonyl, C_{1-24}-alkylaminocarbonyl, di-(C_{1-24}-alkyl)aminocarbonyl, aryl-C_{1-24}-alkoxycarbonyl, aryl-C_{1-24}-alkylaminocarbonyl, C_{1-24}-alkylcarbonyloxymethoxycarbonyl, C_{1-24}-alkylcarbonyloxy-(C_{1-4}-alkyl)methoxycarbonyl, C_{1-24}-alkoxycarbonyloxymethoxycarbonyl, C_{1-24}-alkoxycarbonyloxy-(C_{1-4}-alkyl)-

methoxycarbonyl, all the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds and all the C_{1-4}-alkyl groups of which may be branched or unbranched and saturated or unsaturated, and where each aryl group has the formula II



II

wherein R_3 and R_4 are the same or different and each is selected from the group consisting of hydrogen, halogen, or C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-acyl, C_{1-4}-acyloxy, C_{1-4}-alkoxycarbonyl, all of which may be branched or unbranched; or R_3 and R_4 together form an unbranched saturated alkylene chain having 3 or 4 carbon atoms bound to adjacent positions in the phenyl ring; or R_3 and R_4 together form a methylenedioxy group, a 1,1-ethylidenedioxy group, or a 1,2-ethylenedioxy group bound to adjacent positions of the phenyl ring;

or wherein R_1-CH-CH-R_2 form part of a C_{4-8}-carbocyclic ring which is optionally substituted with hydroxy, mercapto, amino, halogen, oxo, or with C_{1-24}-alkyl, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonyl, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkoxycarbonyl, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino, all the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

or wherein R_1-CH-CH-R_2 form part of the furanose or pyranose ring of a sugar, e.g. D-ribose, D-arabinose, D-xylose, D-lyxose, D-glucose, D-galactose, D-mannose, D-talose, D-

allose, D-altrose, D-gulose, D-idose or the corresponding L-isomers, the hydroxyl groups of which may optionally be replaced by hydrogen, halogen, amino, azido, oxo, mercapto, C_{1-24}-alkoxy, C_{1-24}-alkylthio, C_{1-24}-alkylamino, di-(C_{1-24}-alkyl)amino, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkylcarbonylthio, C_{1-24}-alkylcarbonylamino, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino the C_{1-24}-alkyl groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds;

and physiologically acceptable salts and optical isomers thereof.

2. A compound according to claim 1 wherein R_1 and R_2 each independently are hydrogen or methyl which latter is optionally substituted with hydroxy or mercapto, or with C_{1-24}-alkoxy, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkylthio, or C_{1-24}-alkylcarbonylthio, the C_{1-24}-alkyl and -alkoxy groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds.

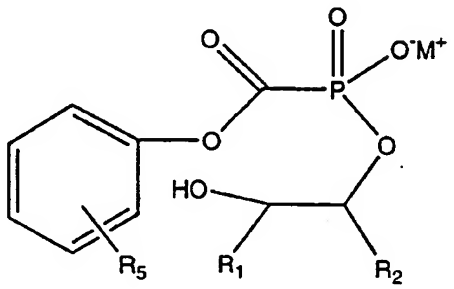
3. A compound according to either of claims 1 or 2 wherein R_1 is methyl which is optionally substituted with hydroxy or mercapto, or with C_{1-24}-alkoxy, C_{1-24}-alkylcarbonyloxy, C_{1-24}-alkylthio, or C_{1-24}-alkylcarbonylthio, the C_{1-24}-alkyl and -alkoxy groups of which may be branched or unbranched and saturated or unsaturated with 1 to 6 double bonds, and R_2 is hydrogen.

4. A compound according to either of claims 1 or 2 wherein R_1 and R_2 each independently are hydrogen or *n*-octadecyloxymethyl.

5. A compound according to any of claims 1 to 4 wherein R_1 is *n*-octadecyloxymethyl and R_2 is hydrogen.

6. A compound according to claim 5 with the (R)-configuration.

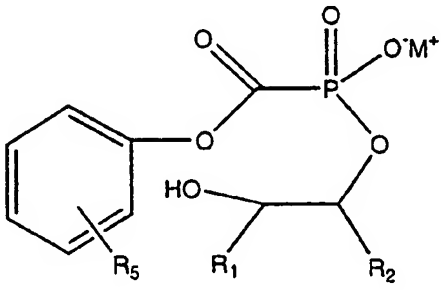
7. A process for the preparation of a compound according to claim 1, characterized by cyclization of a compound of the formula IV



IV

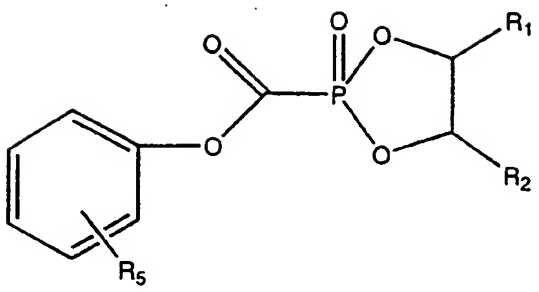
wherein R_1 and R_2 have the meaning given in claim 1 and R_5 is an electron withdrawing group at the *ortho*- or *para*-position of the phenyl ring and M^+ is a cation.

8. A process for the preparation of a compound of the formula IV



IV

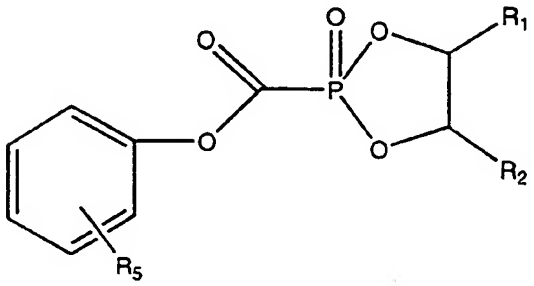
characterized by hydrolysis of a compound of the formula III



III

wherein R_1, R_2, R_5 and M^+ have the same meaning as given above in claim 7.

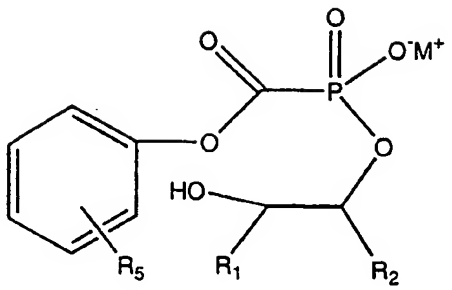
9. A compound of the formula III



III

wherein R_1, R_2 and R_5 have the meaning given in claim 7.

10. A compound of the formula IV



IV

wherein R_1, R_2, R_5 and M^+ have the meaning given in claim 7.

11. A compound according to any of the claims 1 to 6 for use in therapy.

12. A compound according to any of the claims 1 to 6 for use in the treatment of viral infections in mammals.

13. A compound according to any of the claims 1 to 6 for use in the treatment of human herpesvirus or human retrovirus infections.

14. A compound according to any of the claims 1 to 6 for use in the treatment of viral infections in humans caused by HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1 or HLTV-2.

15. Use of a compound according to any of the claims 1 to 6 in the manufacture of a pharmaceutical formulation for the treatment of viral infections in mammals.

16. Use of a compound according to any of the claims 1 to 6 in the manufacture of a pharmaceutical formulation for the treatment of human herpesvirus or human retrovirus infections.

17. Use of a compound according to any of the claims 1 to 6 in the manufacture of a pharmaceutical formulation for the treatment of viral infections in humans caused by HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1 or HLTV-2.

18. A pharmaceutical composition containing as an active ingredient a compound as defined in any one of claims 1 to 6.

19. A pharmaceutical composition according to claim 17 which is suitable for oral administration.

20. A pharmaceutical composition according to claim 17 which is suitable for parenteral administration.

21. A pharmaceutical composition according to claim 17 which is suitable for rectal administration.

22. A pharmaceutical composition according to claim 17 which is suitable for topical administration

23. A method of treatment of virus infections wherein a therapeutically effective amount of a compound according to any of the claims 1 to 6 is administered to a patient in need of such treatment.

24. A method of treatment of human herpesvirus or human retrovirus infections wherein a therapeutically effective amount of a compound according to any of the claims 1 to 6 is administered to a patient in need of such treatment.

25. A method of treatment of viral infections in humans caused by HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1 or HLTV-2 wherein a therapeutically effective amount of a compound according to any of the claims 1 to 6 is administered to a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/02052

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07F 9/6571, C07F 9/6574, C07F 9/40, A61K 31/665
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9615132 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 23 May 1996 (23.05.96) --	1-22
A	J. Am. Chem. Soc., Volume 117, 1995, Thomas C. Bruice et al, "Participation of Two Carboxyl Groups in Phosphodiester Hydrolysis 1. Hydrolysis of Bis(2-carboxyphenyl) Phosphate", pages 12064-12069, see compound 3 --	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 1998	18 -03- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/02052

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-25
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/SE 97/02052

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